



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/SE98/01618 (22) International Filing Date: 11 September 1998 (11.09.98) (30) Priority Data: 9703287-4 11 September 1997 (11.09.97) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): ANDERSSON, Magnus [SE/SE]; Jakob Borgmästares väg 19, S-152 40 Södertälje (SE). LININGTON, Christopher [GB/DE]; Max Plank Institute for Neurobiology, Am Klopferspitz 18 A, D-82152 Martinsried (DE). OLSSON, Tomas [SE/SE]; Lövsundsvägen 47, S-125 40 Älvsjö (SE). WALLSTRÖM, Erik [SE/SE]; Tallspinnarvägen 12, S-125 57 Älvsjö (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PEPTIDES COMPRISING AN IMMUNODOMINANT SEQUENCE DERIVED FROM HUMAN MYELIN OLIGODENDROCYTE GLYCOPROTEIN (57) Abstract There is provided according to the present invention, a peptide comprising an immunodominant sequence derived from human myelin oligodendrocyte glycoprotein (MOG), nucleic acid molecules capable of encoding the peptide and the use of such peptide or nucleic acid in medical therapy or screening.		

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PEPTIDES COMPRISING AN IMMUNODOMINANT SEQUENCE DERIVED FROM HUMAN
MYELIN OLIGODENDROCYTE GLYCOPROTEIN

There is provided according to the present invention, a peptide comprising an immunodominant sequence derived from human myelin oligodendrocyte glycoprotein (MOG), nucleic acid molecules capable of encoding the peptide and the use of such peptide or nucleic acid in medical therapy or screening.

A number of pathological conditions arise from the inappropriate activity of the immune system against host tissue. Such autoimmunity is known to be involved in conditions such as multiple sclerosis (MS) which involves the destruction of the central nervous system (CNS) myelin by T lymphocytes. One protein present in the myelin: myelin oligodendrocyte glycoprotein (MOG), is of particular interest as it is the only myelin autoantigen that produces a complete MS-like disease, in experimental animal models, involving both CNS inflammation and demyelination. Identification of the protein fragments of MOG which are targets for autoreactive immune cells i.e. the immunodominant epitopes may allow these fragments to be used therapeutically.

WO 95/07096 purports to describe methods for the therapy of MS by administration of MOG protein and MOG derived peptides, however it concludes that the important immunological and encephalitogenic determinants of the MOG molecule lie between peptide 35-55.

WO 95/06727 describes the complete sequence of human MOG and proposes its use in the therapy of autoimmune conditions. It also describes a number of MOG fragments which it suggests on the basis of an algorithm may be useful in moderating the autoimmune response. However no indication is given as to whether the predicted peptides do possess significant activity in this regard. No disclosure or suggestion of the peptides of the present invention is made.

The demyelination of the CNS which occurs in MS is mediated by T cells which are responding to particular antigens (autoantigens) present in the myelin sheath. This process involves the uptake and subsequent proteolytic cleavage of the relevant antigen by antigen presenting cells which present the antigen to the T cells in association with a Class II major histocompatibility complex protein . If the T cell epitope of the relevant autoantigen can be identified it can be used to induce non-responsiveness to that autoantigen. This may be done by a variety of known tolerogenic protocols e.g. mucosal tolerance. This offers a therapeutic approach to autoimmune conditions such as MS which depends on the ability to identify the particular immunodominant epitope within the autoantigen which is responsible for eliciting the autoimmune reaction.

Although the above cited prior art suggests the use of MOG proteins in MS therapy, there is no teaching as to which peptides of that protein can be used to obtain a clinically significant effect .

Hence there is a need to identify a MOG peptide which is capable of modulating the autoimmune response occurring in MS patients .

The present inventors have now shown that the sequence of the MOG protein from amino acid 63 to amino acid 87; hereinafter "peptide(63-87)" contains an immunodominant peptide sequence which significantly increases its ability to act as a target for autoimmune cells isolated from patients suffering from MS.

The present invention therefore provides purified peptide (63-87), or immuno-dominant fragments thereof. The sequence of peptide(63-87) is:

PEYRGRTTELLKDAIGEGKVTLRIN.

In a further embodiment of the present invention there is provided a combination comprising a peptide (63-87) of the present invention and one or more sub-dominant MOG peptides. Preferably the sub dominant peptide is selected from peptides:-

5 -GWYRPPPSRVVHLYRNGKDQDGD,
 -IGEGKVTLRIRNVRFSDEGGGFTCFF,
 -RFSDEGGFTCFFRDHSYQEEAAMEL,
 -ENLHRTFDPHFLRVPCW ,
 -FDPHFLRVPCWKITL,

10 and sub dominant epitope peptide fragments thereof .

Also included within the present invention are nucleic acid molecules, preferably DNA molecules capable of encoding a peptide of the present invention and nucleic acid vectors
15 comprising such nucleic acid molecules and cells and cell lines comprising such nucleic acid molecules or vectors . Such nucleic acid molecules, vectors or cells may be used either in the synthesis of a peptide of the present invention, for subsequent administration to a patient or they may be used directly in therapy. For example a naked DNA molecule of the present invention may be administered directly to a patient as part of a therapy known as
20 DNA vaccination (Waisman, A. Nature Medicine, Vol. 2 , 899-905[1996]).

Nucleic acid molecules of the present invention include all redundant sequences thereof i.e. all nucleic acid sequences capable of encoding a peptide of the present invention. The most preferred nucleic acid sequence according to the present invention is that encoding
25 peptide(63-87) which is most preferably:

CCT GAA TAT CGG GGC CGG ACA GAG CTG CTG AAA GAT GCT ATT GGT
GAG GGA AAG GTG ACT CTC AGG ATC CGG AAT.

A pharmaceutical composition comprising a peptide of the present invention and optionally one or more sub-dominant MOG peptides, for use in medical therapy, particularly therapy of multiple sclerosis, is also provided.

5 As used herein the term 'derivative of a peptide' means a peptide derived from another peptide of the present invention by deletion of one or more amino acids, or addition or substitution of one or more amino acids of the peptide with one or more natural or non-natural amino acids, or the chemical modification e.g. glycosylation of the peptide to improve its efficacy and/or pharmacokinetic properties. Such processes of addition,
10 deletion, substitution or modification should be such as not substantially to alter the tolerogenic properties of the peptide. The invention also encompasses peptidomimetics of peptides of the present invention.

As used herein, the term 'isolated peptide' refers to any peptide, irrespective of its method
15 of synthesis, which is locationally distinct from the naturally occurring protein sequence of which it forms a part in nature.

As used herein the term 'medical therapy' includes the treatment, prophylaxis and diagnosis of pathological conditions.

20 In a particular embodiment of the present invention, a peptide of the present invention may be used in the identification of an individual liable to develop symptoms of MS or in the diagnosis of a patient presenting sub-clinical or clinical symptoms of MS. According to this embodiment of the invention, lymphocyte cells removed from an individual may be
25 exposed *in vitro* to a peptide of the present invention and the ability of the peptide to stimulate an immune reaction in the isolated cells may be measured by known techniques, in particular the techniques described in Example 1 hereinafter.

Diagnostic kits comprising a peptide of the present invention are also comprised within the
30 present invention.

The present invention also provides for methods of therapy of autoimmune conditions such as MS, comprising the administration to an individual requiring such therapy of a therapeutically effective amount of a peptide, nucleic acid, cell or cell line of the present invention.

Peptides of the present invention may be generated either using peptide chemical synthesis or when all amino acids of the peptide are naturally occurring amino acids, by recombinant nucleic acid technologies. Both of these technologies are well known to those skilled in the art. The invention also includes processes for the synthesis of peptides, nucleic acids or cell lines of the present invention.

In a further embodiment of the invention there is provided a method of making a peptide of the invention by a chemical process in which individual amino acid residues or fragments of peptides of the invention are joined to form peptide bonds and wherein protecting groups are optionally employed at the beginning and/or end of the process.

The amount of a peptide according to the invention which is required in therapy will, of course, vary and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, and nature of the formulation, the mammal's body weight, surface area, age, and general condition and the particular peptide to be administered. A suitable effective dose of peptides of the invention generally lies in the range of from about 0.0001 $\mu\text{mol/kg}$ to about 1000 $\mu\text{mol/kg}$ bodyweight, preferably from about 0.003 to about 300 $\mu\text{mol/kg}$ bodyweight, e.g. in the range of from about 0.001 to 100 $\mu\text{mol/kg}$ bodyweight, for example, 0.03 to 3.0 $\mu\text{mol/kg}$ bodyweight. The total dose may be given as a single dose or multiple doses, e.g. two to six times per day. For example, for a 75 kg mammal (e.g. a human) the dose range would be about 2.25 $\mu\text{mol/kg/day}$ to 225 $\mu\text{mol/kg/day}$ and a typical dose could be about 100 μmol of peptide. If discrete multiple doses are indicated treatment might typically be 25 μmol of a peptide of the invention given up to 4 times per day. In an

alternative administrative regimen, peptides of the invention may be given on alternate days or even once or twice a week or even less frequently e.g. once a month or once or twice a year. The skilled addressee will appreciate that an appropriate administrative regimen would be at the discretion of the physician or veterinary practitioner.

5

Whilst it is possible for the active peptide to be administered alone, it may be preferable to present the active peptide in a pharmaceutical formulation. Formulations of the present invention, for medical use, comprise a peptide of the invention or a salt thereof together with one or more pharmaceutically acceptable carriers and optionally other therapeutic ingredients e.g. cytokines or other immunomodulating agents which may be conjugated to an active carrier delivery system such as cholera toxin B subunit (CTB) which may provide for improved mucosal uptake.. The carrier(s) should be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and substantially non-deleterious to the recipient thereof. The skilled addressee will appreciate that free acid addition salts (e.g. hydro-halo salts) of peptides referred to herein as well as base salts are encompassed within the ambit of the invention. Most preferably the salts will be pharmaceutically acceptable.

Suitable acid addition salts include those formed from hydrochloric, hydrobromic, nitric, perchloric, sulphuric, citric, tartaric, phosphoric, lactic, benzoic, glutamic, oxalic, aspartic, pyruvic, acetic, succinic, fumaric, maleic, oxaloacetic, isethionic, stearic, phthalic, methanesulphonic, p-toluene sulphonic, benzenesulphonic, lactobionic, glucuronic and trifluoroacetic acids. Suitable base salts include inorganic base salts such as alkali metal (e.g. sodium and potassium) salts and alkaline earth metal (e.g. calcium) salts; organic base salts e.g. phenylethylbenzylamine, dibenzylethylenediamine, ethanolamine and diethanolamine salts; and amino acid salts e.g. lysine and arginine. Most preferably, the salts will be pharmaceutically acceptable.

The present invention, therefore, further provides a pharmaceutical formulation comprising a peptide of the invention together with a pharmaceutically acceptable carrier therefor.

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Naturally, the skilled addressee will appreciate that any pharmaceutical formulation comprising a peptide of the invention can include more than one peptide of the invention. Thus, a pharmaceutical formulation may comprise at least two peptides of the invention or
5 a mixture of peptides of the invention.

There is also provided a method for the preparation of a pharmaceutical formulation comprising bringing into association a peptide, nucleic acid or cell of the present invention, and a pharmaceutically acceptable carrier therefor.

10

A peptide, nucleic acid or cell of the present invention may be administered by any route appropriate to the relevant therapeutic molecule or cell and to the condition to be treated, suitable routes including oral, intra-tracheal, rectal, nasal, topical (including buccal and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intravenous,
15 intradermal, intrathecal, intraperitoneal, and epidural). It will be appreciated that the route may vary with, for example, the condition of the recipient. Preferred formulations are those suitable for oral, nasal or intra-tracheal administration. Most preferred formulations are those suitable for oral administration.

20 Formulations for topical administration in the mouth include lozenges comprising the peptide(s) in a flavoured basis, usually sucrose and acacia and tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouth washes comprising the peptide(s) in a suitable liquid carrier.

25 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, lozenges comprising the peptide(s) in a flavoured base, usually sucrose and acacia and tragacanth; pastilles comprising the active ingredient(s) in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouth washes comprising the active ingredient(s) in a suitable liquid carrier. Each formulation
30 generally contains a predetermined amount of the active peptide(s); as a powder or

granules; or a solution or suspension in an aqueous or non-aqueous liquid such as a syrup, an elixir, an emulsion or draught and the like.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active peptide(s) in a free-flowing form such as a powder or granules, optionally mixed with a binder, (eg povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered peptide(s) moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile.

A syrup may be made by adding the active peptide(s) to a concentrated, aqueous solution of a sugar, for example, sucrose, to which may also be added any necessary ingredients. Such accessory ingredient(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredients, such as a polyhydric alcohol, for example, glycerol or sorbitol.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives, (including antioxidants) and the like.

Emulgents and emulsion stabilisers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate.

Formulations for rectal administration may be presented in any suitable form e.g. as a suppository with a suitable base comprising peptide(s) of the invention in admixture with a neutral fatty base, for example cocoa butter, or, for example in admixture with a salicylate, or in the form of solutions and suspensions. In an alternative, formulations in the form of gelatin rectal capsules comprising active peptide(s) of the invention in admixture with vegetable oil(s) or paraffin oil can be used.

Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns. Where the particle size relates to an active substance in particle form per se, the particle size may be in the range of from 2 to 500 microns. Coarse powder formulations can be administered by rapid inhalation through the nasal passage from a container of the powder held up close to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Thus, peptides of the invention may be formulated in pressurised metered dose inhalers or dry powder inhalers for oral or nasal inhalation or in liquid formulations for nebulisation. The active peptide(s) is micronised or otherwise processed to a particle size suitable for inhalation therapy (mass median diameter $< 10 \mu\text{m}$).

In the case of pressurised metered dose inhalers the micronised peptide(s) can be suspended in a liquefied propellant or a mixture of liquefied propellants. Such propellants can also, but not necessarily act as solvents. In either case, the micronised peptide(s) can be filled into a container equipped, for example with a metering valve.

Suitable propellants include those commonly employed in the art, such as, hydrofluoroalkanes (HFAs). The HFA propellants can be present in any mixture which is appropriate for delivering peptide(s) of the invention to MALT. Examples of suitable HFAs for use in the invention include tetrafluoroethane (eg propellant 134a (Hoechst)) and heptafluoropropane (eg propellant 227 (Hoechst)). Naturally, the skilled addressee will appreciate that appropriate concentrations of surfactants can also be present in such

formulations, for example, sorbitan trioleate, lecithin, oleic acid and the like, the use of surfactants being to increase the physical stability of the peptide(s) preparation. The formulation can also contain solvents, such as ethanol, to improve the solubility of the peptide(s) in the chosen propellant.

5

Active peptides of the invention may be delivered through inhaling devices suitable for dry powder inhalation, such as portable inhaler devices and the like. In such dry powder formulations, the active peptide(s) of the invention can be used either alone or in combination with a carrier, such as lactose, mannitol, or glucose. The selection of carrier is not critical, provided that the physiological action of the peptide(s) of the invention is substantially unimpaired. Other additives may also be included in powder formulations as required e.g. to maintain stability etc. Again, such additives should be such so as not to substantially interfere with the physiological and hence therapeutic effect of the peptide(s) of the invention. The inhaling device can be of any type known in the art, such as a single dose inhaler having a predetermined dose or a multi-dose inhaler wherein the dose is measured by a metering unit within the inhaler or is delivered from an assembly of predetermined doses.

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Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution of a pharmaceutically and pharmacologically acceptable acid addition salt of a peptide(s) of the invention that is isotonic with the blood of the recipient.

20

Useful formulations also comprise concentrated solutions or solids containing peptide(s) of the invention which upon dilution with an appropriate solvent give a solution for parenteral administration as above.

25

EXAMPLE 1

A panel of overlapping synthetic peptides of MOG were screened for their ability to induce
5 IFN γ secretion from peripheral blood lymphocytes obtained from 20 DR2(15)+ MS
patients and 14 DR2(15)+ healthy controls.

The strongest response was observed with MOG peptide 63-87 which, together with the
response to the known MBP epitope 82-104, was highly significant above the background
10 levels of IFN γ secreting cells ($p < 0,01$; figure 1 a b). MOG peptide 38-60, 76-100, 89-113,
162-178 and 168-182 also induced significantly more IFN γ secreting cells than background
levels ($p < 0,05$). When analysing responses in individual patients, most peptides were at the
background level and responding peptides varied between patients. There was however a
dominance also at the individual level for responses to MOG 63-87; which gave responses
15 that were above two standard deviations from the mean group background in 7 of 20 MS
patients (1 of 14 healthy controls). The fact that all peptides showed responses similar to
background levels in at least some patients argues against non-specific peptide stimulation,
supported by the absence of significant MOG peptide responses in the healthy controls. In
both MS patients and healthy controls there were strong responses to positive control PPD
20 and SEB antigens in parallel stimulations.

Claims

1. An isolated peptide comprising the amino acid sequence:
PEYRGRTLLKDAIGEGKVTLRIRN,
5 or an immunodominant peptide fragment thereof.
2. A peptide which is a derivative of a peptide as claimed in claim 1.
3. A peptide according to either of claims 1 and 2, additionally comprising an
10 immunomodulatory peptide sequence.
4. A peptide according to claim 3, wherein the immunomodulatory peptide sequence is a cytokine
- 15 5. A peptidomimetic of a peptide as claimed in any of claims 1 to 4.
6. A nucleic acid molecule capable of encoding a peptide as claimed in any one of claims 1 to 4.
- 20 7. A nucleic acid molecule according to claim 6, wherein the molecule comprises the DNA sequence:
CCT GAA TAT CGG GGC CGG ACA GAG CTG CTG AAA GAT GCT ATT GGT
GAG GGA AAG GTG ACT CTC AGG ATC CGG AAT.
- 25 8. A nucleic acid vector comprising a nucleic acid molecule as claimed in either of claims 6 and 7.
9. A cell comprising a nucleic acid molecule as claimed in either of claims 6 and 7 or a
30 vector as claimed in claim 8.

10. A peptide according to any one of claims 1 to 4 , a nucleic acid molecule according either of claims 6 and 7, a nucleic acid vector according to claim 8 or a cell according to claim 9, for use in medical therapy.

5

11. The use of a peptide according to any one of claims 1 to 4, a nucleic acid molecule according to either of claims 6 and 7, a nucleic acid vector according to claim 8 or a cell according to claim 9 in the preparation of a medicament for use in the therapy of multiple sclerosis.

10

12. A combination comprising a peptide according to any of claims 1 to 4 and one or more peptides selected from:

-GWYRPPPSRVVHLYRNGKDQDGD,

15

-IGEGKVTLRIRNVRFSDGEGGFTCFF,

-RFSDEGGFTCFFRDHSYQEEAAMEL,

-ENLHRTFDPHFRLRVPCW ,

-FDPHFRLRVPCWKITL,

20

and peptide derivatives thereof.

13. A combination according to claim 12 , for use in medical therapy.

25

14. The use of a combination according to claim 12 in the preparation of a medicament for use in the therapy of multiple sclerosis.

15. A method of therapy of multiple sclerosis comprising the administration to a person in need of such therapy of an effective amount of a peptide according to any one of

claims 1 to 4, a nucleic acid molecule according to either of claims 6 and 7, a nucleic acid vector according to claim 8 or a cell according to claim 9.

16. A process for the synthesis of a peptide as claimed in any one of claims 1 to 4,
5 wherein the process comprises the chemical synthesis of a peptide sequence.
17. A process for the synthesis of a peptide as claimed in any one of claims 1 to 4,
wherein the process comprises recombinant nucleic acid technology.
- 10 18. A pharmaceutical formulation comprising a peptide according to any one of claims 1 to 4, a nucleic acid molecule according to either of claims 6 and 7, a nucleic acid vector according to claim 8 or a cell according to claim 9, and a pharmaceutically acceptable carrier therefor.
- 15 19. A diagnostic kit comprising a peptide as claimed in any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01618

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 14/47, A61K 38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CA, MEDLINE, BIOSIS, EMBASE, DBA, REGISTRY,
EMBL/PIR/GENESEQ/SWISSPROT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9506727 A2 (IMMULOGIC PHARMACEUTICAL CORPORATION), 9 March 1995 (09.03.95), page 4, lines 4-7; page 19, lines 30-36; page 21, lines 30-31; page 11, lines 13-18, 23-24; claims 13-16, 18; SEQ ID NO: 50, page 46; SEQ ID,NO: 7, page 36 and the abstract --	1-19
X	WO 9507096 A1 (LA TROBE UNIVERSITY), 16 March 1995 (16.03.95), claim 34 and Figure 7A --	7
X	WO 9612737 A2 (IMMULOGIC PHARMACEUTICAL CORPORATION), 2 May 1996 (02.05.96), claim 45 --	1-11,15-18

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

2 December 1998

Date of mailing of the international search report

10 -12- 1998

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01618

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CAPLUS, CAPLUS accession no. 1995:223904, Amor, Sandra et al: Identification of epitopes of myelin oligodendrocyte glycoprotein for the induction of experimental allergic encephalomyelitis in SJL and Biozzi AB/H mice"; & J. Immunol. (1994), 153(10), 4349-56 --	12-14
P,X	Dialog Information Services, file 155, Medline, Dialog accession No. 09353409, Medline accession no. 98056819, Kerlero de Rosbo N. et al: "Predominance of the autoimmune response to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis: reactivity to the extracellular domain of MOG is directed against three main regions" Eur J Immunol (GERMANY) Nov 1997, 27(11)p3059-69 --	1-19
P,X	WO 9735879 A1 (IMMULOGIC PHARMACEUTICAL CORPORATION), 2 October 1997 (02.10.97), see the claims -- -----	1-19

INTERNATIONAL SEARCH REPORT

international application No.

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body and claim 20 does include an in vivo diagnostic method, the search has been carried out and based on the alleged effects of the compound (c.f. PCT Rule 39.1(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/11/98

International application No.

PCT/SE 98/01618

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